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Development of a Leukemia Therapy Using Antisense Oligonucleotides Directed Against Homeobox Genes

Most leukemias are thought to be caused by aberrant expression of certain genes with oncogenic potential. Many of these genes are known to regulate the proliferation of hematopoietic cells, and intuitively, it makes sense that leukemias are caused by aberrant expression of genes which control proliferation. Therefore, uncontrolled expression of such genes causes uncontrolled proliferation of hematopoietic cells, namely leukemia.

Much of the current leukemia therapy rests on chemotherapy. However, in the last few years, a method to directly control the expression of such genes has been achieved for certain oncogenic genes. This technique involves the use of very short single stranded DNA molecules (called antisense oligonucleotides) which recognize specifically the targeted oncogenic gene.

I (and others) have recently identified a new class of genes, homeobox genes, which appear to regulate proliferation of hematopoietic cells. Uncontrolled expression of some homeobox genes may account for some leukemias. I have shown that two, HLX and DLX-1, are expressed in most acute myelogenous leukemia cell lines.

In the research project described here, I intend to determine whether antisense oligonucleotides directed against the HLX and DLX-1 gene can inhibit the growth of leukemia cells *in vitro*. I intend to test their effectiveness against cells obtained from patients with acute and chronic myelogenous leukemias. These studies will show whether or not homeobox antisense oligonucleotides can be used to treat leukemias.

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Regulation of P-Glycoprotein by Protein Kinase C

This study will examine the role of phosphorylation in the modulation of the activity of the multidrug transporter, P-glycoprotein, the product of the *MDR*1 gene. A recombinant protein model system will be employed that utilizes the baculovirus expression of P-glycoprotein in insect cells to study its regulation *in vitro* by protein kinases such as protein kinase C. The positive regulatory effect of phosphorylation on the drug transport and drug binding activities of P-glycoprotein will be examined. These studies should give a clearer understanding of the ability of phosphorylation to increase the activity of P-glycoprotein activity and hence, elevate multidrug resistance, a process that compromises the response of leukemic patients to chemotherapy by a wide variety of structurally unrelated anticancer drugs. This study will also test the ability of protein kinase inhibitors to reverse phosphorylation and the multidrug resistance phenotype and to help define a new class of potential anticancer agents.